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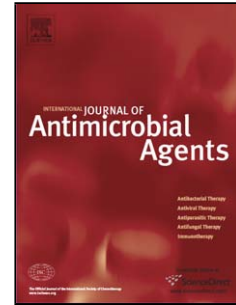
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Travellers and viral haemorrhagic fevers: what are the risks?

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Abstract

Viral haemorrhagic fevers (VHF) are caused by zoonotic viral infections transmitted to humans directly or by ticks or mosquitoes. The overall risk to travellers is conservatively estimated at <1 in 1 million travel episodes to African countries where infection is present, and febrile patients returning from these countries are at least 1000 times more likely to have malaria than Lassa fever or another VHF. No cases have been reported in fellow travellers exposed to a travelling case and only one asymptomatic seroconversion (to Lassa) has been reported in over 2000 contacts following care of VHF cases in modern Western hospital settings. However, healthcare-associated transmission of infection has been a major problem in some endemic settings. The potential for healthcare-associated infection and the threats posed by unrecognized or new agents necessitate a high index of suspicion and a standardized risk assessment approach to febrile travellers. Travel-related hantavirus infections are increasingly being reported from Europe and the Americas. This article summarizes the epidemiology and reports of travel-related VHF cases in the past 40 years, together with strategies for their recognition, management and prevention.

Keywords:

Travel

Viral haemorrhagic fever

Epidemiology

Risk prevention

Vaccine

Zoonosis

1. Introduction

Viral haemorrhagic fevers (VHF) rarely infect travellers but raise concern because of their potential for a dramatic clinical picture, high mortality, nosocomial transmission and risk to laboratory personnel. Historically, they have been major impediments to military campaigns over the centuries and remain endemic in much of the world, with emerging outbreaks in new locations and recent descriptions of new diseases. In response to travel-related cases of Lassa fever in the USA and the UK, and the importation of Marburg infection into Germany and the former Yugoslavia, proscriptive guidelines for the public health response to imported cases of suspected VHF and their clinical and laboratory management were developed in the 1970s [1]. These have been reinforced in a recent European consensus statement [2,3]. Several VHF agents have been weaponized and their continued potential for deliberate release has been emphasized [2,4,5].

The purpose of this review is to focus on the risks of acquiring a VHF during travel and to update lists of known importations of cases across national borders.

Epidemiological and clinical approaches to the management of returned travellers with fever are also discussed. Full clinical descriptions of each infection are beyond the scope of this article but can be accessed from recent reviews. Dengue [6,7] is excluded from this review and only passing mention will be made of the many VHFs that have localized geographical niches and that have not been reported as being travel related.

2. Methods

We conducted reviews of the Medline/PubMed databases for the period 1966–2009, the online database Google Scholar and the ProMED database using the keywords

'travel', 'traveller' and 'imported' combined with the terms 'VHF' and 'viral haemorrhagic fever' and with each of the diseases being described. In addition we reviewed relevant sections of the websites of the US Centers for Disease Control and Protection (www.cdc.gov), Health Canada (www.hc-sc.gc.ca/index-eng.php), the UK Health Protection Agency (www.hpa.org.uk), the English National Travel Health Network and Centre (www.nathnac.org) and the World Health Organization (www.who.int/en). Standard textbooks of infectious diseases and travel medicine were consulted, together with appropriate reviews and recently published books about VHF [8,9] and infections in military settings [10].

We cross-correlated references from these sources, when possible including papers in all languages. We list the source references for each case of VHF reported to have crossed an international boundary and highlight key references for further reading on clinical and epidemiological management. Laboratory-acquired cases have not been tabulated, nor have infections arising as a result of animal importation.

3. Epidemiology

3.1. General features

The agents causing VHF are RNA viruses in the families Arenaviridae, Bunyaviridae, Filoviridae and Flaviviridae. All are known or thought to be zoonoses, some associated with very specific hosts, vectors and locations, such as the South American arenaviruses, and some with a larger range of animal hosts and wider intercontinental distribution, such as Crimean–Congo haemorrhagic fever (CCHF). Key epidemiological features of VHF known to have affected international travellers are summarized in Table 1.

[Table 1 here]

The routes of transmission of VHF to man in nature can be categorized into three broad groups [11]. The first includes infections that are only transmitted by arthropod vectors, such as yellow fever (YF) and most other flaviviruses, and are not usually spread from person to person. The second group includes agents spread to man by contact with uncooked meat, blood, urine, saliva and other secretions of animals, such as arenaviruses, hantaviruses and filoviruses. Contamination of foodstuffs or human habitation by rodent urine has been implicated in the spread of arenavirus and hantavirus infections, but the zoonotic transmission routes to man of filovirus infections remain less clear (see below). The third group, which includes the bunyaviruses causing CCHF and Rift Valley fever (RVF), may be spread by arthropod vectors or by body-fluid contact.

In general, the human populations at most risk in endemic areas are pastoralists, butchers, slaughterers and others who have close contact with animals, their products and their ticks; people living in housing with peri-domestic rodent infestation; and those with occupations that take them into areas with enzootic transmission, such as mining, engineering, forestry work, cane cutting and agricultural labourers. Traditional funeral practices and close domestic contact can also result in infection in these settings. Civil unrest, conflict and political changes leading to the displacement of populations and breakdown of public health systems have been implicated in epidemics of VHFs such as CCHF and Marburg. Changes in climate conditions leading to increases in rodent hosts favour the spread of hantavirus infections in Europe [12] and epidemics of RVF have followed heavy rains and consequent increases in mosquito vectors in Egypt and Kenya [8]. Similar

conditions and alterations in land use may also account for some of the recent expansion of CCHF in South and Eastern Europe [13].

3.2. Infection in endemic settings

Hospital-associated transmission of infection has been responsible for the amplification of local outbreaks of several VHFs in Africa, including Ebola, Marburg and Lassa. Poor infection control measures and the reuse of sharps has resulted in onward transmission of infection to patients and staff in these settings. Other risks to staff and visitors include close contact and subsequent contamination with body fluids of patients, and mucocutaneous exposure to blood, saliva and respiratory secretions, especially during resuscitation or procedures that create infectious aerosols. This includes splashes of blood and other fluids into the mouth or eyes. Droplet spread of respiratory secretions may also play a small role.

In general, dramatic outbreaks of nosocomial infection within endemic areas have been terminated by the provision of adequate medical supplies and training staff in the proper use of personal protective equipment, together with enforcement of guidance about the safe handling of deceased patients [14]. The risks of contact infection and nosocomial infection in high-income settings are discussed in more detail later in this review. Patients, expatriates and local healthcare staff sent to Europe or the USA for medical care are included in Tables 2 and 3, which list individual cases of VHFs that have travelled internationally.

3.3. Infections in travellers

Other travellers whose occupations or leisure activities bring them into contact with settings at risk for VHF are at particular risk; this includes both international travellers and those who do not cross national borders. Camping, hiking and other rural

holiday pursuits may expose travellers to ticks and mosquitoes or to rodent urine, while occupations such as mining, geological field work and cave exploration can result in contact with animal hosts. Military and peacekeeping personnel on active duty in the field are at risk if they are exposed to rodents, ticks or mosquito vectors. Mass gatherings can increase the risk of any infection, and the annual Hajj pilgrimage is of theoretical concern because it is accompanied by massive importation of animals for slaughter [15].

Lassa fever was the first VHF to be identified in a traveller and is the most common imported VHF, with 28 cases documented in the past 30 years (Table 2). At least nine were healthcare workers in Africa and most of the remainder had rural occupations, including aid workers and military personnel. These infections all occurred in West Africa, especially Nigeria and Sierra Leone, with the first reported case from Mali in 2009. In 2008 a novel Old World arenavirus, Lujo virus, caused the death of a Zambian resident and the paramedic who assisted in her transport to South Africa for medical care [43]. Two nurses who attended the patients in South Africa also became infected, together with a hospital cleaner. Only the nurse who received ribavirin survived. The natural reservoir, geographical range and distribution of subclinical human infection with this new virus have yet to be determined, but the sequence of events is a reminder of the dangers of unrecognized illness due to VHF.

[Table 2 here]

Only a few cases of imported filovirus infection have been reported. Table 3 includes two patients who travelled within Kenya, illustrating the link between these infections in travellers to cave exploration and bat exposure, in addition to an outbreak of Marburg infection in miners exposed to bats [84]. Fruit bats have now been

confirmed to carry Marburg and Ebola infections, although the mode of transmission to people has not been determined [85,86]. Other large non-human primates can also be infected, and some human filovirus infections have been epidemiologically linked with the local preparation or consumption of non-human primate 'bushmeat'.

[Table 3 here]

Given the large geographical range of CCHF in Africa, Eastern Europe, the Middle East and central Asia as far as Xiang Xiang Province in China, it is surprising that more travel-related infections have not been reported. Most cases have involved proven or possible exposure to ticks, including crushing ticks with unprotected fingers (Table 3). The recent acquisition of a lethal infection by an American serviceman in Afghanistan emphasizes the need to consider CCHF in the differential diagnosis of fever from this area [57].

Similarly, few clinical cases of RVF have been reported in travellers until recently, apart from two cases returning to the West for expert care of ophthalmic complications of infection and a patient in whom RVF may have contributed to death due to acute hepatitis A (Table 3). Subclinical cases have been identified in peacekeeping and military personnel stationed in endemic areas [59,61].

Hantaviruses are found in most continents and caused epidemics of haemorrhagic fever with renal syndrome (HFRS) in civilians and troops during World War I and the Korean War [10]. Recent reports of infected travellers in Europe and Asia again include both military and civilian personnel (Table 3). The European forms of HFRS have been reported in peacekeepers in the Balkan region, and travel-related cases are being reported more often from Western Europe and Scandinavia, especially in campers. The need for reference laboratory testing was emphasized by a recent

'pseudo-importation' of hantavirus from Ecuador to Belgium, subsequently shown to have been acquired after return to Belgium [80]. In the New World, several new infections leading to hantavirus pulmonary syndrome (HPS) have been recognized, and a few travel-related cases have been reported (Table 3).

Yellow fever (YF) was a major cause of death of early European travellers to West Africa and was taken to the Americas with the slave trade [10]. From the 17th to the end of the 19th century tens of thousands of British, French, Dutch and Spanish troops were killed by YF outbreaks in the Caribbean and Central American region, and importation of YF to the USA was a constant problem, with onward transmission by local populations of *Aedes* mosquitoes. Mosquito bite avoidance measures and vaccination have been available for almost a century, but ten imported cases have been reported in the last three decades, usually in tourists who had not been vaccinated (Table 4).

[Table 4 here]

*3.4 Animal travel and VHF*s

Animal movements have been implicated in the spread of CCHF in central Asia [98] and the Arabian peninsula [99,100], of RVF into Saudi Arabia and the Yemen [101] and possibly in the recent emergence of human infections with Alkhurmah virus, a novel flavivirus similar to Kyasanur Forest disease in western Saudi Arabia [102].

The risk of animal importation to the West was exemplified by outbreaks of Marburg disease involving 31 people, including 6 secondary cases, in Frankfurt, Marburg and Belgrade in 1967 [103], traced to monkeys used to provide tissue for cell-culture lines. Asymptomatic seroconversions have occurred in animal handlers looking after macaque monkeys imported from the Philippines, resulting in transmission of a strain

of Ebola within a primate facility in Reston, Virginia [104], and in pig handlers in the Philippines [105]. Imported rodent cell lines have been the source of hantavirus infections in laboratory workers in the UK [106]. In the past, importation of infected mosquito vectors has been implicated in the transmission of YF, and this should be prevented by spraying aircraft that come from endemic areas [107].

4. Clinical features

VHF are severe infections with high mortality rates in travellers (Tables 2–4), apart from Puumala virus forms of HFRS from Europe. Details of clinical features in endemic settings and in travellers are beyond the scope of this review but can be found in textbooks and the references cited. The onset of most infections is abrupt, often with severe malaise and headache in the early stages, sometimes resembling encephalitis. Severe infections often follow a biphasic course, with initial improvement followed by multisystem failure in the second week, including encephalopathy. Haemorrhagic features can be absent at presentation in a substantial minority of patients and are rarely seen in the northern European forms of HFRS, or in patients with HPS or RVF. A fine rash may be seen in the first week of filovirus infections, and pharyngitis and/or facial swelling in patients with Lassa fever. Jaundice can be prominent in YF and RVF. Abdominal pain can be severe in patients with Ebola, Marburg or CCHF, and prostration is a prominent feature of Ebola. Ophthalmic problems can complicate RVF (retinitis) and Lassa (uveitis), which also causes deafness. Spontaneous abortion is a feature of Lassa, Ebola and CCHF.

The differential diagnosis is wide and includes respiratory infections in the early stages, as well as malaria, dengue and other arboviruses, enteric fever, viral hepatitis, leptospirosis, meningococcaemia, encephalitis and rickettsial infections.

Most infections cause neutropenia, thrombocytopenia, proteinuria and raised transaminases, plus other laboratory abnormalities related to the infecting organism, such as renal failure with hantaviruses causing HFRS. Specific diagnosis largely rests on virus culture or rapid molecular tests; serological methods may help in acute cases, but are mainly useful in convalescence. Such tests should only be performed by prior arrangement with national reference centres [3].

Treatment is largely supportive, including dedicated high-security intensive care [3,5]. Ribavirin (unlicensed for these purposes) has proven beneficial when given early in Lassa fever and is used for other arenavirus infections. It appears to be useful in CCHF in areas where mortality is high, although its role remains controversial [108]. It confers no benefit in filovirus infections.

5. Risks assessment and management of returned travellers

5.1. Healthcare settings

Risk assessment to inform the management of patients returning from overseas with febrile symptoms should assess the likelihood that their illness is because of VHF, the likelihood of the infection being transmitted to workers, and the seriousness of the outcome of such transmission. The risks of delaying diagnosis and treatment of other treatable infections such as malaria should also be incorporated in the risk assessment process.

Firstly, how common are these infections? The overall risk to travellers is conservatively estimated at <1 in 1 million travel episodes to African countries where infection is present. In the recent GeoSentinel review of returned travellers with febrile illness managed in specialist centres around the world, VHF was not diagnosed in 6957 patients, of whom 2559 had returned from sub-Saharan Africa

[109]. Malaria was the most common diagnosis, as it was in 14/23 (61%) of patients specifically screened for VHF in London in the early 1980s [110] and in 14/37 (38%) travellers with possible VHF risk more recently at the London Hospital for Tropical Diseases [111]. Africa, especially West and central Africa, has been the origin of most imported cases of VHF but is also the most common origin for severe malaria imported to Europe and North America [109] and there is a remote possibility that a traveller might have both. During the decade 2000–2009, four patients have imported VHFs to the UK (Tables 2 and 3), compared with 17 109 cases of malaria [112], and 4061 cases of enteric fever notified 2000–8 (mostly imported) [113].

More detailed risk assessment of the returned traveller with a febrile illness, especially with a rash, jaundice or haemorrhagic manifestations that cannot otherwise be explained, should take into account the countries visited, the specific areas visited within the country, and activities that might have put them at risk, including rural work and leisure pursuits such as cave visits and mining; contacts with wild animals, especially bats, rodents or their excreta; and working in or attending a health facility as a patient. The incubation period is taken into account, as none of the transmissible VHFs in Africa have an incubation period longer than 21 days. If the onset of symptoms has occurred more than 21 days after leaving an endemic area, the risk of VHF can be excluded [2,111]. Patients at medium or high epidemiological risk should be isolated and discussed with national clinical, laboratory and public health experts. Initial investigations beyond exclusion of malaria should be kept to a minimum. If malaria is excluded, hence increasing the possibility of a VHF causing the illness, the intensity of isolation can be escalated, according to local or national guidelines.

Although regulations have been in force in the UK since 1976 [1,114], they are rarely applied systematically, even in specialist units. A travel history is only obtained from about 10% of patients with fever attending busy emergency rooms in the north-west of England (unpublished audit), and only a minority of patients thought to have potentially transmissible infections are isolated in British emergency rooms [115]. A recent survey of 21 British infectious disease units revealed that written VHF protocols available in six units were only systematically followed in two units; eight others discussed VHF risks in unit guidelines, and seven had no written protocols [111]. One concern voiced by specialists is that use of such protocols might increase the delay in diagnosing falciparum malaria, which can rapidly be fatal and should be treated immediately [116,117]. However, an audit of delays in diagnosis made at the London Hospital for Tropical Diseases, where use of the VHF assessment protocol is embedded in daily practice, only showed an increase in time to laboratory diagnosis of malaria from a median 90 min (range 50–125) for patients not thought to be at VHF risk to 140 mins (101–225) for those assessed as having a possible VHF [111].

The next issue is the risk to personnel attending the patient. In a review of contact tracing for nine patients admitted to Western facilities with Lassa fever, no clinical illness was seen in 1521 contacts, including fellow travellers and healthcare workers [118]. One German physician (who had received ribavirin prophylaxis) had an asymptomatic seroconversion after failing to use adequate barrier precautions, yielding an estimated transmission risk of 0.06% [118]. To this may be added 576 further healthcare contacts screened after recently imported cases of Lassa to the UK, with no secondary cases [34,41,42]. No clinical cases were found after surveillance of almost 400 contacts of Marburg [47,48], 74 contacts of Ebola [50] or 245 contacts of CCHF [53,56] in recent travellers. Concern lingers, however,

because of the theoretical risk of aerosol dispersion of some infections, reinforced by the apparent remote airborne spread of the Ebola–Reston virus to non-human primates, and transmission of asymptomatic infections to animal handlers. Several excellent reviews include further details about healthcare-associated risks and the specific precautions that are necessary to reduce them [1,3,4,34,118,119,120,121].

To summarize, a VHF should be considered in a traveller with fever $\geq 38^{\circ}\text{C}$ that starts within 21 days of leaving a risk area, especially if they have any of the risk exposures detailed earlier, and a severe illness with haemorrhagic manifestations, rash or other features, such as jaundice, that are compatible with a VHF and cannot be explained by malaria or other conditions. Such patients should be isolated in a single room, preferably with negative pressure, and attendants and diagnostic sampling kept to a minimum. Healthcare workers should adopt precautions against contact with blood and secretions, including gloves, gowns and eye protection, and against droplet spread of infection. Care should be taken to avoid contamination during removal or safe disposal of personal protective equipment. Suspected cases should be discussed immediately with appropriate local public health personnel and national clinical experts, who will assist with determining the future epidemiological, diagnostic and clinical management of the patient and contacts. This might include transfer to a special isolation facility [3,34].

Although no cases of transmission have been documented as a result of routine diagnostic laboratory processing of specimens from returned travellers, clinical laboratories should be warned that there is a known or potential VHF risk and diagnostic sampling kept to a minimum. The closed systems used in modern clinical haematology and biochemistry laboratories should be safe. Samples should be transported safely and handled in appropriate safety cabinets by adequately trained

personnel. Apart from risks of direct exposure to blood and other fluids and tissues, there is a potential risk of aerosol dissemination. Specific virological tests should only be performed in designated laboratories by personnel trained to use biosafety level 4 containment facilities. There is a high risk to mortuary personnel and undertakers. All contacts with patients or samples should be identified and categorized according to their exposure risk [3,34,41,42,111].

5.2. Risks for fellow travellers and family contacts

Outside endemic areas and settings, fellow travellers have never been known to contract a VHF from another infected traveller. In the past, heroic efforts have been made to trace fellow travellers across international boundaries, such as following the importation of Lassa fever to the USA, with no evidence of transmission in several hundred potential contacts [21]. Within endemic areas, close family contact (excluding the preparation of bodies for burial) has been implicated in the transmission of most VHFs originating in Africa, but this has only been documented in Western settings for Marburg infection transmitted sexually to a female spouse, and in South America for Argentinean haemorrhagic fever [4] and Andes HPS virus [122]. Sexual transmission of other viruses, particularly Lassa, Ebola, CCHF, other arenaviruses and hantaviruses remains undocumented, but both Lassa and Ebola have been detected in semen 3 months after infection [4,8].

6. Prevention for travellers

6.1. General

Many resources are available to inform travellers about potential health risks at their destination and while travelling. Healthcare workers who plan to work in an area endemic for a VHF should familiarize themselves with local risks and appropriate

protective measures. Travellers in areas with mosquito-borne VHFs such as YF and RVF should take precautions to reduce the risk of bites, predominantly by *Aedes* mosquitoes, which are daytime and dusk feeders. This includes wearing long-sleeved shirts and long trousers, and using repellents. Tick bites can be minimized by tucking trousers into socks and impregnating clothes with permethrin, and by avoiding direct contact with animals such as sheep, cattle and goats. Travellers potentially exposed to ticks should inspect themselves regularly and remove any attached ticks carefully, avoiding crushing the tick or handling it with unprotected fingers. Ticks are more easily seen on pale-coloured clothing. In Africa, travellers should not handle or eat non-human primate-derived 'bushmeat' and should not handle or consume uncooked meat, blood or secretions (including unpasteurized milk) from animals in CCHF- or RVF-endemic areas.

Campers and others travelling or working in rural areas should avoid contact with rodents or their excreta and should wear masks if it is essential to sweep out habitations infested by rodents in any area where Lassa or other arenaviruses or hantaviruses are prevalent. In light of current knowledge, contact with fruit bats or their habitations, such as caves in Africa, should also be avoided.

6.2. Immunization

The only approved vaccine against a VHF in travellers is for YF, although unlicensed or restricted vaccines have been used for RVF and in some areas against HFRS agents. YF vaccination may be required under international health regulations by individual countries as a condition of entry, and/or recommended to prevent acquiring YF. Unfortunately, the information provided by tour companies and travel agents to travellers visiting YF risk areas may not accurately discuss the risk and

requirements for vaccination. Of the 10 imported cases reported in the last 30 years, only one had been immunized (Table 4).

Although the risk of YF infection in travellers to West Africa has been estimated to be higher than that in travellers to endemic areas of South America [87], 4 of the 10 cases in Table 4 had been to the Americas. Recent expansion of YF transmission in South America, along with the recognition of rare but life-threatening adverse events following YF vaccine, especially in those aged 60 and older [123], emphasize the need to improve the definition of YF risk areas. Geographic mapping of risk based on review of human and non-human primate cases, YF serology, vegetation, altitude and vector distribution has been undertaken by a World Health Organization (WHO) working group. They will harmonize internationally accepted maps of risk areas published by WHO and the Centers for Disease Control and Prevention, with clearer definitions of level of risk and vaccination recommendations down to small geographical zones. These maps should be available by the end of 2010.

7. Conclusions

The risk of a traveller acquiring a VHF is extremely small, but the consequences for them and for those involved in their care are potentially devastating. Patients with an imported VHF often have contact with many healthcare personnel before their diagnosis is recognized, but no clinically significant cases of transmission to healthcare attendants have been recorded in modern Western hospital settings. Nevertheless, it is important to take adequate travel histories from patients with fever and perform a more specific risk assessment for patients returning from areas endemic for a VHF. Management of suspected cases should follow national protocols. Travellers need to be informed about the health risks associated with their travel plans, and to take steps to reduce personal risk.

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Table 1

Epidemiological features of viral haemorrhagic fevers (VHF) reported in travellers 1969–2009

Virus family VHF	Reservoir	Transmission	Main risk areas	Main traveller populations at risk	Incubation period (days)
Arenaviridae					
Lassa fever	Rodents	Infected rodent contact Inhaled aerosol rodent urine Ingested rodent excreta Rodent excreta on broken skin Healthcare and laboratory	West Africa	Missionaries and aid workers Healthcare workers Rural travellers Military	5–6
Lujo	Unknown	Unknown Healthcare	Sub-Saharan Africa	Unknown Healthcare workers	7–13 ^a
Filoviridae					
Marburg	Uncertain Fruit bats Other primates probable secondary host	Bats, caves and mines Healthcare Laboratory	Sub-Saharan Africa	Miners and tourists in caves Healthcare workers	3–16
Ebola	Uncertain Fruit bats	Healthcare Laboratory	Sub-Saharan Africa	Healthcare workers Zoologists	3–16
Bunyaviridae					
Crimean– Congo haemorrhagic fever	Livestock (cattle, sheep, etc.)	Tick (<i>Hyalomma</i>) bites Crushing ticks Contact with blood/fluids of infected animals Healthcare	Sub-Saharan Africa, former Soviet Union, South and East Europe, Middle East, Eurasia, western	Rural travel Aid workers Military	3–12

China

Rift Valley fever	Livestock	Mosquito bites (<i>Aedes</i>) Contact with blood/fluids of infected animals Unpasteurized milk Needlestick and laboratory	Sub-Saharan Africa, Middle East	Military on rural postings	2–5
Haemorrhagic fever with renal syndrome (HFRS)	Rodents (striped field mice, yellow-necked mice, rats, or bank voles)	Aerosols of rodent urine, excreta, saliva and from contaminated dust, nesting materials etc. Laboratory	Worldwide, but mainly in East Asia and Europe	Campers, hikers etc. Military	9–35
Hantavirus pulmonary syndrome	Rodents	Aerosols of rodent urine, excreta, saliva etc., as HFRS Laboratory	North and South America	Hikers, farm visitors etc.	7–28
Flaviviridae					
Yellow fever	Monkeys Humans in urban cycles	Mosquito bites (<i>Aedes</i> , also in Americas <i>Haemagogus</i>) Needlestick and laboratory	West, sub-Saharan and East Africa Central and South America	Rural travellers (unvaccinated)	3–6

^a Based on few cases only.

Table 2Lassa fever in travellers, 1969–2009^a

Year	Country of origin	Imported to	Age (years)	Gender	Profession	Fatal	Comment	Reference
1969	Nigeria	USA	52	F	Nurse	No		[17]
1971	Sierra Leone	UK	NS	F	Nurse	No	Retrospective in 1972	[18]
1971	Sierra Leone	UK	NS	M	Physician	No	Retrospective in 1972	[18]
1972	Sierra Leone	UK	35	F	Nurse	No		[19]
1974	Nigeria	Germany	33	M	Physician	No		[20]

1975	Sierra Leone	USA	39	F	Aid Worker	No		[21]
1975	Nigeria	UK	39	M	Physician	Yes	Death day 8	[20,22]
1976	Nigeria	UK	NS	M	Engineer	No		[22]
1976	Sierra Leone	USA	43	F	Aid Worker	No		[21]
1980	Burkina Faso	Netherlands	34	M	Aid Worker	No		[23]
1981	Nigeria	UK	18	F	Teacher	No		[24]
1982	Nigeria	UK	21	F	Diplomat	No		[25]
1984	Sierra Leone	UK	NS	M	Geologist	No		[26]
1985	Sierra Leone	UK	27	F	Nurse	No		[27]
1987	Sierra Leone	Japan	48	M	Engineer	No		[28]

1987	Sierra Leone, Liberia	Israel	47	M	Engineer	No		[29]
1989	Nigeria	Canada	38	M	Agricultural work	No		[30]
1989	Nigeria	USA	43	M	Engineer	Yes	Death day 14	[31]
2000	Burkina Faso, Côte d'Ivoire, Ghana	Germany	23	F	Tourist	Yes	Death day 15	[32]
2000	Sierra Leone	UK	50	M	Aid Worker	Yes	Death day 30	[33,34]
2000	Nigeria	Germany	57	M	Nigerian National	Yes	Death day 16	[35]
2000	Sierra Leone	Netherlands	48	M	Physician	Yes	Death day 16	[36]

2003	Sierra Leone	UK	NS	M	Soldier	No		[37]
2004	Sierra Leone, Liberia	USA	38	M	Businessman	Yes	Death ~ day 7	[38]
2006	Sierra Leone	Germany	68	M	Tourist	No		[39]
2007	Nigeria	S. Africa	46	M	Physician	No	Re-reported in 2009	[40]
2009	Nigeria	UK	66	M	Retired	Yes	Death day 23	[41]
2009	Mali	UK	20s	M	Working	Yes	Death day 11	[42]

^a Updated after Macher and Wolfe 2006 [16].

NS, not stated.

Table 3

Viral haemorrhagic fevers in travellers, 1969–2009, excluding Lassa and yellow fever

Agent	Year	Country of origin	Imported to	Age (years)	Gender	Fatal	Comments	Ref.
Arenaviruses								
Lujo	2008	Zambia	S. Africa	36	F	Yes	Safari agent Four secondary cases in HCW, of whom three died (one below)	[43]
Lujo	2008	Zambia	S. Africa	33	M	Yes	Paramedic who assisted patient above	[43]
Filoviruses								
Marburg	1975	Zimbabwe	S. Africa	20	M	Yes	Australian tourist – secondary cases in girlfriend and nurse, both survived	[44]
Marburg	1980	Kenya – Kitum Cave	Kenya – Nairobi	56	M	Yes	French engineer Secondary case (physician) survived	[45]
Marburg	1987	Kenya – Kitum Cave	Kenya	15	M	Yes	Danish tourist, extensive travel	[46]
Marburg	2008	Uganda – Python Cave	Netherlands	41	F	Yes	Tourist, visited Python Cave, Maramagambo Forest 120 contacts, no	[47]

							130 contacts, no seroconversions/illness	
Marburg	2008	Uganda – Python Cave	USA	44	F	No	Tourist, visited Python Cave and diagnosed retrospectively No illness in ~260 contacts (220 HCW)	[48]
Unknown filovirus	1990	Kenya	Sweden	21	M	No	Tourist – typical filovirus features but virus not confirmed	[49]
Ebola	1994	Côte d’Ivoire	Switzerland	34	F	No	Scientist who did chimpanzee autopsy No seroconversions in 74 contacts	[48]
Ebola	1996	Gabon	S. Africa	NS	M	No	Physician – secondary case in nurse, who died	[51]
Bunyaviruses								
CCHF	1985	Zaire (DRC)	S. Africa	48	M	Yes	Cattle-farm exposure	[52]
CCHF	1986	Tanzania	S. Africa	26	M	No	Possible tick bites	[52]
CCHF	1997	Zimbabwe	UK	78	F	Yes	Tourist to farm near Harare No illness among 60 contacts	[53]
CCHF	2001	Bulgaria	Germany	NS	NS	No	Tourist	[54]
CCHF	2004	Senegal	France	60	F	No	Medical technician 181 contacts screened, no	[55,56]

							181 contacts screened, no secondary cases	6]
CCHF	2009	Afghanistan	Germany	22	M	Yes	US soldier	[57]
RVF	1979	Kenya	Saudi Arabia, Canada	41	F	No	Canadian expatriate, diagnosis in Saudi Arabia, ophthalmology reviews in Canada	[58]
RVF	1979	Egypt	Sweden	NA	NS	No	Eight soldiers, fever serosurveillance	[59]
RVF	1981	Tanzania	Netherlands	57	F	No	Expatriate, for ophthalmic care	[60]
RVF	2001	Chad	France	NA	M	No	Two symptomatic soldiers, fever serosurveillance	[61]
RVF	2008	Kenya	Germany	71	F	Yes	Tourist with fatal hepatitis A and probable RVF	[62]
HFRS	1986	S. Korea	[USA]	NA	M	Yes	Of 14 symptomatic US soldiers 10 were hospitalized with 2 deaths	[63]
HFRS	1987	Malaysia	UK	47	M	No	Businessman with Far East strain	[64]
HFRS	1988	Belgium	[Canada]	46	M	No	Canadian soldier living next to forest	[65]
HFRS	1988	Germany	USA	24	M	No	Soldier Puumala virus	[66]

HFRS	1990	Germany	[USA]	NA	M/F	No	US military exercise outbreak; 16/23 cases symptomatic Puumala virus	[67]
HFRS	1991	Romania	France	NS	M	No	Working with laboratory rats Seoul or similar virus	[68]
HFRS	1992	Bosnia	Croatia	24	M	No	Canadian UN worker Seoul virus	[69]
HFRS	1995	Bosnia	UK	19	M	No	Soldier with severe respiratory and renal disease Seoul virus	[70]
HFRS	1995	Croatia	Czechoslovakia	28	M	No	Soldier with severe disease requiring dialysis Strain uncertain	[71]
HFRS	1996	China	Taiwan	38	M	No	Led to finding hantaviruses in Taiwan	[72]
HFRS	1996	Bosnia	USA	NA	M	No	Two soldiers – one symptomatic, one found on serosurveillance	[73]
HFRS	1999	France	Belgium	37	M	No	Camping Puumala virus with HPS	[74]
HFRS	2002	Romania, Balkan countries, NS	Italy	NS	M	No	'Young man' Puumala virus with HPS	[75]

HFRS	2003	Central Europe, NS	Spain	32	M	No	Trucker Puumala virus	[76]
HFRS	2005	Sweden	Croatia	41	M	No	Holiday home in forest Puumala virus	[77]
HFRS	2005	S. Korea	[USA]	NA	M	No	Four symptomatic soldiers in rural areas	[78]
HFRS	2006	Serbia	Germany	65	M	No	Rural holiday home Dobrava virus	[79]
HFRS	2009	(Ecuador) Belgium	Belgium	22	F	No	Pseudo-importation of Puumala virus acquired on return to Belgium	[80]
HPS	1997	Bolivia	Chile	20	M	Yes	Backpacking, rural Laguna Negra virus	[81]
HPS	2001	Chile, Argentina	France	58	M	No	Botanist in rural Chile and Argentina Virus not isolated, serology only	[82]
HPS	2006	Bolivia	Canada	15	F	Yes	Tourist on farms with rodent droppings Andes virus	[83]

CCHF, Crimean–Congo haemorrhagic fever; DRC, Democratic Republic of Congo; HCW, healthcare worker; HFRS, haemorrhagic fever with renal syndrome (hantavirus); HPS, hantavirus pulmonary syndrome; NA, not applicable; NS, not stated; RVF, Rift Valley fever.

Table 4Yellow fever in travellers, 1970–2009^a

Year	Country of infection	Imported to	Age (years)	Gender	Profession	Fatal	Vaccinated	Ref.
1979	Senegal	France	42	M	Tourist	Yes	No	[88]
1979	Senegal	France	25	M	Tourist	Yes	No	[88]
1985	Guinea-Bissau, The Gambia, Senegal	Netherlands	27	F	Tourist	No	No	[89]
1987	Niger, Mali, Burkina Faso, Mauritania	Spain	37	F	Tourist	No	Yes	[90]
1996	Brazil	Switzerland	53	M	Tourist	Yes	No	[91,92]

1997	Brazil	USA	45	M	Tourist	Yes	No	[93]
1999	Côte d'Ivoire	Germany	39	M	Cameraman	Yes	No	[94]
1999	Venezuela	USA	48	M	Tourist	Yes	No	[95]
2001	The Gambia	Belgium	47	F	Tourist	Yes	No	[96]
2002	Brazil	USA	47	M	Tourist	Yes	No	[97]

^a updated after Monath and Cetron 2002 [87].